DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
94358d
Central Region

Food and Drug Administr
Waterview Corporate Ce
10 Waterview Blvd., 3rd
Parsippany, NJ 07054

Telephone (973) 526-6009

October 3, 2003

WARNING LETTER

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Mr. Paul D. Cottone
President and CEO
PLIVA, Inc.
72 Eagle Rock Avenue
East Hanover, New Jersey 07936

File No.: 04-NWJ-02

Dear Mr. Cottone:

During April 10 through June 20, 2003, investigators from this office conducted an inspection of your drug manufacturing site, located at 17 West Street, East Hanover, New Jersey. Our investigators documented significant violations of the current Good Manufacturing Practice (cGMP) Regulations found in Title 21, Code of Federal Regulations (CFR), Parts 210 and 211, for drug products manufactured and tested at this site. These violations cause those products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

1. The inspection revealed significant deficiencies in the Quality Control Laboratory which fails to meet the requirements of 21 CFR 211.192, as follows:

   a. Out-of-specification (OOS) results were invalidated, without a thorough investigation, supporting data, documentation, or justification. For example:

      - Confirmed OOS results for [redacted] (preservative) assay used in Cyclosporine Soft Gel Capsules USP 100mg Lots 32041143 and 32060466, were invalidated by Quality Assurance, that concluded that the chromatographs were incorrectly integrated. The chromatographs were reprocessed with adjusted baseline parameters, yielding acceptable results, and the lots were released for distribution. However, the laboratory investigation concluded that the results could not be invalidated and that no problems were observed during the chromatographic run.

- An OOS content uniformity result, obtained during validation testing of Vospire (Albuterol Sulfate) 4mg Extended Release Lot 7542003, was invalidated by the quality control laboratory that concluded that the OOS result was caused by the deterioration of the HPLC system. However, there is no data or documentation to support this conclusion and all system suitability requirements were met during the initial sample run. Testing was repeated with new samples, yielding acceptable results and the lot was released. In addition, there was no investigation conducted to determine if variations in the manufacturing process could have attributed to the OOS result. Passing data for Lot 7542003 was used to support the validation of this product.

- A confirmed OOS result for blend assay testing was obtained for Metoclopramide HCl Tablets, 5 mg, Lot 5172031. Subsequently, new blend samples were tested using a newly developed in-house method that yields acceptable results. The firm invalidated the initial confirmed OOS result without justification. In addition, the firm did not investigate the OOS result from Lot 5172033 used as a control during the retest of Lot 5172031. Both lots were subsequently released.

b. There was no further testing or confirmation for initial OOS results obtained during dose uniformity testing of Albuterol Aerosol MDI 90ug. The investigation remains incomplete as to possible cause and effect on other batches. In addition, there was no written investigation for the following eight lots of product. For example:

   - An OOS result was obtained for sample 8 of Lot 8012026 during a manufacturing and testing campaign. The dose uniformity testing was discontinued/aborted for lots 8012027 – 8012029, although samples 1-7 had been tested for each lot. Lots 8012026 – 8012029 remain in quarantine since May 2002.

   - A testing campaign was aborted when three content uniformity results for Lot 8012058 were at the specification limit. Lots 8012056 – 8012059 remain in quarantine since June 2002.

c. Confirmed OOS results for blend uniformity were obtained and no failure investigations have been performed by the Production and Technical Service units. For example, no further investigation was conducted for the OOS results obtained and confirmed during the blend uniformity testing of Fluoxetine Capsules 20mg Lots 6483006, 6483009 and 6483010. Additionally, there was no evaluation of the impact of these failures on other batches of this product currently on the market.

2. Scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity have not been established [21 CFR 211.160(a)]. For example:

   a. Your procedures allow for the averaging of individual OOS results with in-specification results to arrive at a passing average. For example, during blend assay testing of Metoclopramide HCL Tablets, Lot 5172004, individual OOS results were averaged with in-specification results.

   b. Not all analytical test methods detect known impurities for all raw materials. For example, Trazodone HCl drug substance supplied by a specific manufacturer has a known impurity. However, test method RM1-8300-00 has not been demonstrated to detect this impurity in this supplier's material. Three lots of Trazodone HCl have been received from this supplier and approved for use in finished product lots.

3. Laboratory records do not include complete data derived from all tests including a record of all calculations performed in connection with the test [21 CFR 211.194(a)(5)]. For example, in process tablet weights and calculations generated during friability testing are recorded on scrap paper and transferred to the batch record. The original raw data is then discarded and could not be verified.

4. Written procedures describing the handling of all written and oral complaints regarding a drug product were not followed [21 CFR 211.198]. Not all product quality complaints are investigated by the Quality Assurance Department as required by your procedure, QA-004F, Customer Complaints. For example, complaint # 2003-009, concerning an empty can of Albuterol Aerosol MDI, 90ug, Lot 8012022A, was not investigated by Quality Assurance. After the complainant's sample was received on February 21, 2003, and subsequently misplaced, no testing or further investigation was conducted.

5. Equipment used in the manufacture, processing, packing, or holding of a drug product was not of appropriate design [21 CFR 211.63] in that a diverter shield, welded into the [redacted] mixer bowl (#0899), was observed to be rusted and not suitable for use. This equipment is used in the production of Pentoxifylline 400mg Tablets and Naproxen 375mg and 500mg Delayed Release Tablets. Review of the cleaning records for this equipment did not note the rusting of the diverter shield.

The above items are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts.

We have received your firm's written response, dated July 8, 2003, concerning the Form FDA 483 Inspectional Observations issued at the conclusion of the inspection. Your response indicates that procedures for conducting and reviewing laboratory investigations are being revised. During the inspection the investigators noted that as a general practice, out-of-specification results were invalidated based on laboratory investigations only and not extended to deviations in the manufacturing process, which could have been a factor. Your response now includes subsequent reviews of the manufacturing process in several instances. We still have some concerns regarding the rationale of invalidating confirmed laboratory results during the investigation process.

Regarding Observation 1A, the documented laboratory investigation did not provide a rationale for reprocessing the chromatograms. Your response does not explain how the parameters were selected for the reprocessed chromatograms. Regarding Observation 1B, your response that the deteriorating HPLC system resulted in the OOS result, is inconsistent with the testing data that indicated all system suitability requirements were met during the run. Regarding Observation 1E, your response references that a new assay method was implemented as an enhancement to the original blend assay, which ultimately yielded in-specification results for the lot tested. Your response does not provide the justification for invalidating the original OOS result, which was confirmed by re-injection.

Regarding Observation 2A, your response still does not provide the rationale for aborting the dose uniformity testing campaign, based on higher than expected results from test injections, which were used to establish retention times and integration parameters. Regarding Observation 2B, your response references intermittent failures of the air conditioning system, causing higher temperature spikes in the laboratory, which adversely affected test results. During the inspection, no documentation was provided to the investigators to support this theory.

Regarding Observation 3C, your response cited sample collection techniques for the OOS results in dose uniformity testing, however it does not provide an adequate rationale for invalidating the original results. It should be noted that testing methods, including sample preparation procedures, should be thoroughly tested and validated before they are used to test and release products.

Please be advised that pre-approval coverage was also conducted during this inspection, for [redacted] Based on the results of this inspection and the FDA483 Inspectional Observations concerning these applications issued at the conclusion of the inspection, [redacted] Notification of final agency action on the application will be issued from FDA's Center for Drug Evaluation and Research.

Your additional response should include any corrective action taken with regard to these applications.

You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office in writing within 15 working days or receipt of this letter of any further corrective actions you plan to implement to address the deficiencies at your firm. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the timeframe within which corrective actions will be completed.

Your reply should be addressed to the Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Mercedes Mota, Compliance Officer, with a copy addressed to Nancy Rolli, Pre-Approval Manager.

Sincerely,

Edward-H-Wilkens, for

Douglas I. Ellsworth
District Director
New Jersey District